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10/516,741	08/15/2005	Thomas Jespersen	4528-0109PUS2	6986

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

NOTIFICATION DATE	DELIVERY MODE
11/05/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,741	JESPERSEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7-14* is/are pending in the application.

4a) Of the above claim(s) *3 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2 and 7-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-3 and 7-14 are pending

Claims 3, 10 (with respect to the non-elected species), 12 (with respect to the non-elected species) and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention,

Claims 1-2 and 7-13 are under examination.

Withdrawn Rejection

In view of the amendments to the claims and applicants' arguments the 35 USC 112 first and second paragraph rejections; the 35 USC 102(e) over Gillespie are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 7-13, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is indefinite as the body of the claim is inconsistent with the preamble. The body of the claim recites isolating mRNA that shows a change in electrophysiology of the cell. The preamble recites identifying a heterologous DNA.

2. It is not clear whether a DNA library or a member derived from the library that comprise the different heterologous DNA sequence is being claimed in step (ii).

Claim Rejections - 35 USC § 102/103

Claims1-2 and 7-13, as amended, are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Qin (6994993).

Qin discloses at col. 20, line 1 up to col. 22, line 50:

> The present invention provides a whole cell or isolated cell membrane method to detect compound modulation of human .beta.1A sodium channel subunit.
>
> The method comprises the steps;
>
> 1) contacting a compound, and a cell or isolated cell membrane that contains functional human .beta.1A sodium channel subunit, and
>
> 2) measuring a change in the cell or isolated cell membrane in response to modified human .beta.1A sodium channel subunit function by the compound.
>
> The measurement means... can be defined by comparing a cell or cell membrane that has been exposed to a compound to an identical cell or cell membrane preparation that has not been similarly expose to the compound. Alternatively two cells, one containing functional human .beta.1A sodium channel subunit and a second cell identical to the first,

but lacking functional human .beta.1A sodium channel subunit could be both used. Both cells or cell membranes are contacted with the same compound and compared for differences between the two cells.

Particularly preferred cell based assays (or cell membrane assays, if suitable) are those where the cell expresses an endogenous or recombinant sodium .alpha. channel subunit simultaneously with recombinant human .beta.1A. In these assays, a putative modulating compound can be analyzed for its effect on electrophysiological changes to the sodium flux upon the cell for altered expression of beta1A expression, or altered expression of the alpha/beta1A complex. Cells expressing recombinant human beta 1A are subjected to electrophysiological analysis to measure the total influx of sodium ions across the cell membrane by way of voltage differential using techniques well known by artisans in the field and described herein, including patch clamp voltage techniques ….. Compounds that affect the proper function of human beta 1 may increase or decrease the capacity to open the Na channel, may increase or decrease the rate of Na influx (thus affect the change of membrane potential), may increase or decrease the rate of desensitization or re-sensitization of the channel. The term "test compound" or "modulating compound" as used herein in connection with a suspected modulator of human beta1A refers to an organic molecule that has the potential to disrupt specific ion channel activity or cell surface expression of human beta 1A. For example, but not to limit the scope of the current invention, compounds may include small organic molecules, synthetic or natural amino acid peptides, proteins, or synthetic or natural nucleic acid sequences, or any chemical derivatives of the aforementioned.

The term "cell" refers to at least one cell, but includes a plurality of cells appropriate for the sensitivity of the detection method. Cells suitable for the present invention may be bacterial, yeast, or eukaryotic. For assays to which electrophysiological analysis is conducted, the cells must be eukaryotic, preferably selected from a group consisting of Xenopus oocytes, or PC12, COS-7, CHO, HEK293, SK-N-SH cells.

The term "high throughput" refers to an assay design that allows easy analysis of multiple samples simultaneously, and capacity for robotic manipulation…..Examples of assay formats include 96-well or 384-well plates, levitating droplets, and "lab on a chip" microchannel chips used for liquid handling experiments.

The cellular changes suitable for the method of the present invention comprise directly measuring changes in the function or quantity of human.beta.1A sodium channel subunit, or by measuring downstream effects of human beta.1A sodium channel subunit function, for example by measuring secondary messenger concentrations or changes in transcription or by changes in protein levels of genes that are transcriptionally influenced by human beta.1A sodium channel subunit, or by measuring phenotypic changes in the cell. Preferred measurement means include changes in the quantity of human beta.1A sodium channel subunit protein, changes in the functional activity of human beta.1A sodium channel subunit, changes in the quantity of mRNA….. **Changes in the levels of mRNA are detected by reverse transcription polymerase chain reaction (RT-PCR) or by differential gene expression.**

The present invention is also directed to methods for screening for compounds that modulate the expression of DNA or RNA encoding Human beta.1A sodium channel subunit as well as the function of Human beta.1A sodium channel subunit protein in vivo. Compounds may modulate by increasing or attenuating the expression of DNA or RNA encoding a Human beta.1A sodium channel subunit, or the function of a Human beta.1A sodium channel subunit protein. Compounds that modulate the expression of DNA or RNA encoding a Human beta.1A sodium channel subunit or the function of a Human beta.1A sodium channel subunit protein may be detected by a variety of assays.

See also the abstract and the specific steps of the method in the Examples starting at col. 29, Example 1. (All emphasis added).

Claims1-2 and 7-13, as amended, are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Maher (6969449).

Maher discloses at e.g., col. 12, line 30 up to the Examples, particularly Example 10:

1) Instrumentation including electrodes, and electrode arrays for reliably generating uniform electrical fields in cultures of living cells in aqueous solution.

2) Multiwell plates comprising surface electrodes for high throughput and miniaturized stimulation and analysis of ion channel or cellular activities.

3) Systems for high throughput analysis of ion channel and cellular activities and for use in drug discovery, analysis, screening and profiling.

4) Methods for modulating the transmembrane potential of a living cell via the use of repetitive electrical stimulation.

5) Methods for screening the effects of test compounds on the activities of voltage regulated, and non-voltage regulated ion channels, transporters and leak currents. Including determining state-dependent pharmacological activity of compounds against ion channel and transporter proteins.

6) Methods for profiling and selecting cells or clones based on their response to electrical stimulation.

7) Methods for quantitative determination of cellular and ion channel parameters in a high-throughput manner, and for quantification of the pharmacological effects of compounds on those parameters.

8) Methods for the introduction of exogenous compounds into the intracellular spaces of cells.

9) Methods for modulating the transmembrane potential of intracellular organelles, and for screening test compounds against ion channels in these organelles.

10) Methods for characterizing the physiological effect of the transmembrane potential on the function and regulation of physiological and biochemical responses, including gene expression, enzyme function, protein activity and ligand binding.

11) Methods for programming or training adaptive neuronal networks or bio-computers for specific functional or logical responses.

12) Methods for providing efficient neuronal interfaces for prosthetic devices implanted into an animal, including a human.

Selection of stable clones will typically be made on the basis of successful expression of the ion channel of interest at sufficient level to enable it's facile detection. **In many cases this analysis will require functional characterization of individual clones to identify those that exhibit appropriate electrophysiological characteristics consistent with expression of the clone of interest. This analysis can be completed via the use of patch clamping** .....

The invention also provides non-human animals expressing one or more hybrid olfactory receptor sequences of the invention, particularly human olfactory receptor sequences. Such expression can be used to determine whether a test compound specifically binds to a mammalian olfactory transmembrane receptor polypeptide in vivo by contacting a non-human animal stably or transiently infected with a **nucleic acid derived from the library of the invention with a test compound and determining whether the animal reacts to the test compound by specifically binding to the receptor polypeptide.**

Response to Arguments

Applicants acknowledged that Qin describes cells being transfected with cDNA or mRNA molecules encoding a Sodium gated/31A subunit and the subsequent measurement of biological activity using electrophysiological techniques including in response to a test agent. Maher describes multiwell electrode assemblies that can be used to study cells transfected with the DNA/mRNA encoding an ion channel and the subsequent analysis of the electrophysiological profile of the ion channel being studied. But argued that none of the three cited documents describe the analysis of multiple different DNA molecules as part of the same assembly. Each of these documents describes the analysis of cells (either singly or multiple cells) each containing the same heterologous DNA expressing a single defined ion channel. Claim 1 of this application requires that a plurality of cells, each containing a different heterologous DNA, that is a member of a DNA library. The presently claimed invention differs from the prior art because the cited prior art does not describe the subsequent isolation of mRNA only from cells exhibiting some form of electrophysiological phenotypic change. Moreover, the present claims are non-obvious over the cited documents because each of the cited documents only describe the study of a single ion channel deriving from one

heterologous DNA molecule. There is no suggestion to study multiple different proteins expressed from multiple heterologous proteins. Qin describes cells being transfected with cDNA or mRNA molecules encoding a Sodium gated/31A subunit and the subsequent measurement of biological activity using electrophysiological techniques including in response to a test agent.

Applicants' arguments regarding the analysis of multiple different DNA molecules as part of the same assembly is not commensurate in scope with the claims, which does not recite an assembly. Nonetheless, attention is drawn to Maher at **e.g.,** col. 77, Example 17 which discloses the screening of multiple channels of sodium, calcium, potassium in a multiple cells of HL5. Furthermore, Maher discloses the different types of cells that express the different channels. Likewise, Qin teaches or at least suggests that sodium gated/31A subunits which would read on the claimed library. Furthermore, Qin teaches as stated above the measurement using mRNA.

Thus, each of the cited prior art either positively teaches, at least suggests, pluraliry of cells transfected by different heterologous genes of ion channels as tuahgt by Maher or can be implied by the teachings of Qin using different subunits. Qin above, for example, teaches that "..measurement

means include changes….. in the quantity of mRNA….. **Changes in the levels of mRNA are detected by reverse transcription polymerase chain reaction (RT-PCR) or by differential gene expression.**

No claim is allowed.

Conclusion

This application contains claims 3, 10, 12 (for non-elected species) and 14 drawn to non-elected invention and species. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
October 26, 2007